REMARKS

The present response is intended to be fully responsive to all points of objection and/or rejection raised by the Examiner and is believed to place the application in condition for allowance. Favorable reconsideration and allowance of the application is respectfully requested.

Status of Claims

Claims 19-39 were pending in the application. Claims 19-30 were withdrawn. Claims 1-15, 17, and 18 are canceled herein without prejudice or disclaimer. New claims 31-39 are added herein. Support for this amendment can be found, at least, in the claims as filed and pages 26-37 of the specification.

EXAMINER INTERVIEW

Applicants note that Applicants' representative Prakash Subbiah spoke with Examiner Kapushoc over phone on March 25, 2010. Applicants thank the Examiner for his courtesy during the telephonic interview. Specifically, Applicants discussed the claim features in new claim 31. The Examiner noted that he would consider removing the rejections after receiving this Response. No agreement was reached for allowance.

CLAIM OBJECTIONS

In the Office Action, the Examiner objected to claim 10 as being improper dependent form because independent claim 1 already contains the limitation "cardiac transplant." In response, Applicants note that Applicants have canceled this claim without prejudice, and therefore the objection is now moot.

CLAIM REJECTIONS

Rejections Under 35 U.S.C § 112, Second Paragraph

In the Office Action, the Examiner rejected claims 14-16 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Specifically, the Examiner asserts that the phrase "said underexpressed genes" in claims 14 and 15 does not have antecedent basis and the phrase "cullin 4A" alone is not consonant with its gene symbol. In response, Applicants note that Applicants have canceled these claims without prejudice, and therefore the rejection is now moot. Applicants further note that new claims do not contain the aforementioned phrases.

Rejections Under 35 U.S.C § 112, First Paragraph

In the Office Action, the Examiner rejected claims 1-18 under 35 U.S.C. § 112, first paragraph, as failing to comply with enablement requirement. Specifically, the Examiner asserts that the specification does not disclose any expression level, sample type, tissue type for a standard, and they are unpredictable in light of statistical variations and thus require undue experimentation. Applicants respectfully traverse this rejection.

Applicants note that Applicants have canceled these claims without prejudice or disclaimer, and thus the rejection is now moot.

Applicants further note that Applicants have added new claims 31-39, in an effort to advance the prosecution. Claim 31 recies "[a] method for identifying a cardiac transplant tissue rejection in a *human* subject, said method comprising: determining a *first gene expression profile* in a *blood sample* taken from said *human* subject, wherein said first gene expression profile comprises the *nucleic acid expression level* of an ubiquinol-cytochrome c reductase binding protein (UQCRB); and comparing said first gene expression profile to a pre-determined *second gene expression profile*, wherein said second gene expression profile comprises the *nucleic acid expression level* of UQCRB derived from blood samples collected from a human cardiac transplant population that does not have cardiac tissue rejection, wherein a statistically significant increase in

UQCRB expression in said first gene expression profile compared to said second gene expression profile is an indicative of cardiac transplant tissue rejection in said human subject." [emphasis added]. The specification fully enables one of skill in the art to determine a gene expression profile for identifying a cardiac transplant tissue rejection.

For example, the specification demonstrates multiple methods of determining the amount of gene expression and explains numerous statistical tools for correlating the values with transplant rejection. *See* page 6, lines 22-27 and page 8, line 27 through page 9, line 4 of the specification. In particular, Example 1 shows expression data from microarray method as well as qRT-PCR method. *See* page 27, lines 7-27 and page 29, lines 10-22. Form these test data, it is merely a routine statistical task for one of skill in the art to identify a standard value for comparison so as to determine prediction or identification of transplant rejection, as claimed.

In addition, the specification describes selecting patient population and analyzing data using various statistical tools. *See* page 26, lines 4-5 and 18-28, page 28 line 20 through page 29, line 7, and figures 1-4. Specifically, the specification explains as follows:

> The probability of selecting a set of 91 candidates by chance was estimated. 91 genes were randomly selected, a determination of gene concordance was made, with the total number of concordant genes in the randomly selected group computed. This process was repeated 10000 times, and a p-value was determined, reflecting the probability of a chance occurrence of the observed or better concordance... The capacity of candidate markers to distinguish Control, Rejection, and Post-Rejection samples was assessed using hierarchical clustering. Clusters were constructed using average linkage clustering and Pearson correlation coefficients as a measure of similarity using Cluster software and displayed using Treeview software.

See page 28 line 20 through page 29, line 7.

Accordingly, the specification provides an example of a statistical selections, correlations, and statistical-significance (p) values. Additionally, the specification explains the expression as follows:

> In another embodiment, the term "expression" refers to the transcription and stable accumulation of sense (mRNA) or antisense RNA derived from the nucleic acid fragment or fragments of the invention. Expression may refer in one embodiment, to translation of mRNA into a polypeptide.

See page 7, lines 19-22 of the specification.

Clearly, the specification teaches one of skilled in the art how to determine the expression profile. In addition, the Specification clearly shows that the expression of UQCRB was 2.25 fold higher (225%) in transplant rejection samples, compared to control samples. *See* page 33, Table 2. Based on this level of higher degree of difference in the expression level, one of skilled in the art can readily ascertain that UQCRB alone is sufficient to identify a cardiac transplant tissue rejection in a human subject.

Only the most basic and routine task would therefore be required to determine a statistically significant difference between a control expression profile and a sample expression profile. This is greatly underscored when taking into account that statistical tools for identifying the standards were well known in the art and also explained in the specification, as set forth above. It is well known and routine in the art to apply statistics on different values of raw data to determine their significance and thereby identify a threshold limit of a standard. Statistical methods are well known and also explained throughout the specification, as discussed above. While some statistical testing may be necessary to compare to standard, such test for data on mere five genes is not undue.

Furthermore, the Examiner has failed to set forth a case that undue experimentation would be required to practice the invention across the full scope of the instant claims. It is the Examiner that bears the burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by a claim is not adequately enabled by the description of the invention in the specification. *In re Wright*, 9 U.S.P.Q.2d 1510, 1512-1513 (Fed. Cir. 1993) (citing *In re Marzocchi*, 169 U.S.P.Q. 367, 369-70 (CCPA 1971)).

The above-discussed teachings in Applicants' specification are more than adequate to enable the full scope of the invention and cannot properly be ignored. While Applicants acknowledge this would require some routine testing and statistical analysis,

"[e]nablement is not precluded by the necessity for some experimentation such as routine [testing]." *In re Wands*, 858 F.2d at 737. Some amount of experimentation is permissible, especially when the specification "provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id.* (quoting *Ex parte Jackson*, 217 USPQ 2d 804, 807 (Bd. App. 1982)). Such is the case here, where only routine testing is required and extensive guidance is provided. Additionally, the experimentation described by Applicants is inarguably typical in the art, and not undue. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165 at 1174.

Finally, Applicants need not disclose all possible values of the expression levels. The legal standard for enablement does not require that Applicants demonstrate enablement for all possible claimed iterations. Enablement must bear only a reasonable relationship to the scope of the claims. *See* MPEP 2164.01(b) (citing *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (CCPA 1970)). For example, a patent applicant is not required to "predict every possible variation, improvement or commercial embodiment of his invention." *United States Steel Corp. v. Phillips Petroleum Co.*, 673 F. Supp. 1278, 1292 (D. Del. 1987), *aff'd,* 865 F.2d 1247, 1250 (Fed. Cir. 1989) (specifically quoting this statement).

Accordingly, the withdrawal of the rejection under 35 U.S.C. §112, first paragraph for lack of enablement is respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, the pending claims are deemed to be allowable. Their favorable reconsideration and allowance is respectfully requested.

Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below. Similarly, if there are any further issues yet to be resolved to advance the prosecution of this application to issue, the Examiner is requested to telephone the undersigned counsel.

Please charge any fees associated with this paper to deposit account No. 50-3355.

Respectfully submitted,

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